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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,972	DOUCETTE-STAMM ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,17-20 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *17-20* is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13,17-20 and 32-34* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Restriction

1. The response to restriction filed on 8/16/05 and 8/18/05 is acknowledged. Applicant elected Group 1, claims 1-13 and 32 drawn to DNA with respect to SEQ.ID.NO: 2580 and SEQ.ID.NO: 6352.

The restriction requirement is traversed with respect to the restriction of the claims of Group I from the claims of Group III. Applicants submit that a search of a nucleic acid would be coextensive of a search the polypeptide that it encodes. Thus, there is no serious burden to keep the claims to the polypeptide (Group III) with the claims for the nucleic acid (Group I). Accordingly, Applicants respectfully request that the claims of Group III (claims 17-20 drawn to polypeptides) be rejoined with the claims of Group 1, as no serious burden has been evidenced by the Office. Applicant also states that searching a nucleic acid and encoding polypeptide does not constitute a serious burden on office and is no serious burden to keep the claims that are drawn to DNA with the claims of polypeptide.

Applicant's arguments filed on 8/18/05 have been fully considered but they are not deemed to be persuasive.

MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner. Thus the first element for restriction is independent or distinct invention and the second element for restriction is search. With respect to the first element, the examiner has established the restriction based on M.P.E.P 803, 806.04 and 806.05. See 37 C.F.R. 1.142 as the claims of Groups I and III are drawn to patentably distinct inventions or independent inventions namely DNA and polypeptide as fully stated in the previous office action.

With respect to the second element, the examiner again disagrees with the applicant because the nucleic acid database search, the protein database search and the literature search for group I and III are particularly relevant in this art, are not co-extensive and are much more important in evaluating the burden of search. Further, it is doubted that applicants would readily accept the rejection of one invention by the application of art teaching another invention. Clearly different searches and issues are involved in the examination of each group. Burden in examining materially different groups such as DNA and polypeptide having materially different issues (for example: 35 U.S.C. 112 first paragraph) also exist.

Should applicants traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention(s). Therefore, the restriction between DNA and polypeptide in pursuant to 35 U.S.C. 121 and 37 CFR 1.141 is proper and made final.

Status of claims

2. Claims 5, 9, 10, 32 and 33 have been amended.

Claims 14-16 and 21-31 are canceled.

Claims 1-13, 17-20 and 32-34 are pending.

Claims 1-13 and 32-34 are under examination.

Claims 17-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 8/16/05.

Priority

3. This application 10/724,972 is a division of 09/450,969 filed 11/29/99 which is a continuation in part of 09/134,001, filed 8/13/98 Patent Number: 6,380,370 which claims priority from provisional application 60/064,964 filed on 11/08/1997.

Information Disclosure Statement

4. The Information Disclosure Statement submitted on 12/1/03 is reviewed and a signed copy of the same is attached to this Office action.

Sequence Rule Non-compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 for the reason(s) set forth below:

It is noted that page 79 contains nucleic acid sequences (more than 10 nucleic acids). However, they are not identified by sequence identification numbers. Any sequences recited in the instant specification which are encompassed by the definitions for nucleotide and/or amino acid sequences as set forth in 37 C.F.R. 1.821(a)(1) and (a)(2) must comply with the requirements of 37 C.F.R 1.821 through 1.825. All SEQ ID numbers recited in the specification and/or the claims must be included in the Sequence Listing. Note that branched sequences are specifically excluded from this definition.

Full compliance with the sequence rules is required in response to this office action.

Specification Informalities and objections

6. Applicant is advised to update the status of all application whether pending or patented.

7. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure without complete evidence that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of biological materials.

Applicant is advised to provide a copy of ATCC: 55998 deposit information for this application. Since there are several applications, each with a different SEQ.ID.NO from a genomic sequence of *S.epidermidis* has been filed in the Office and these applications have been assigned to various examiners in 1600 technology Center. it is not clear whether the claimed sequences are part of the ATCC deposit or something else.

Since the ATCC: 55998 deposit information is not present in the application, it is not clear whether the expression vector comprising the SEQ.ID.NO: 2580 and the corresponding amino acid sequence SEQ.ID.NO: 6352 are part of the sequences submitted under ATCC: 55998 deposit or not.

The specification lacks complete information on how to make expression vector (pET page 74) carrying properly cloned *S.pneumoniae* having the nucleotide sequence SEQ.ID.NO: 2580 (1008 nucleic acids) that encodes the protein SEQ.ID.NO: 6352 (335 amino acids). It is not clear whether the expression vector carrying the claimed sequences can be reproducibly isolated from without undue experimentation. It is noted that this vector could be used in all those claims, which broadly recite a nucleic acid carrying vector.

Because one skilled in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the vector comprising the claimed nucleic acid sequence of the invention, a suitable deposit for patent purposes, evidence of public availability of the vector of the invention or evidence of the reproducibility without undue experimentation of the monoclonal antibodies is required.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required. As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1) The name and address of the depository;
2) The name and address of the depositor;
3) The date of deposit;
4) The identity of the deposit and the accession number given by the depository;
5) The date of the viability test;
6) The procedures used to obtain a sample if the test is not done by the depository; and

7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-13 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the revised guidelines on written description available at www.uspto.gov (O.G. published January 30, 2001). This is a written description rejection.

The claims are drawn to an isolated nucleic acid or immunogenic composition comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide comprising SEQ ID NO: 6352, an isolated nucleic acid sequence comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide or fragment thereof, wherein said nucleic acid is SEQ ID NO: 2580. Claims are also directed to an isolated nucleic acid comprising a nucleotide sequence of at least 8 nucleotides that hybridizes under high stringency conditions to SEQ ID NO: 2580, an isolated nucleic acid comprising a nucleotide sequence, wherein the nucleotide sequence hybridizes under high stringency conditions to SEQ ID NO: 2580 or its complements, a recombinant expression vector and host cell comprising said sequences.
Recitation of "isolated DNA sequence encoding a polypeptide comprising SEQ.ID.NO: 6352 " in the claims is interpreted as isolated DNA encoding a polypeptide which comprises a part of SEQ.ID.NO + unlimited/unknown sequence. Similarly, recitation of "a polypeptide" or "a nucleic acid" in the claims is viewed as something less than the polypeptide or less than the nucleic acid sequence.

The specification teaches an isolated nucleic acid sequence as set forth in SEQ.ID.NO: 2580 (1008 nucleic acid sequence), an isolated nucleic acid (i.e., SEQ.ID.NO: 2580) encoding the *S.epidermidis* polypeptide comprising the amino acid sequence SEQ.ID.NO: 6352 (335 amino acid sequence). However, the specification does not disclose an isolated DNA sequence encoding a polypeptide comprising SEQ.ID.NO: 6352 and unlimited/ unknown sequences, isolated nucleic acid comprising SEQ.ID.NO: 2580 + unlimited/ unknown sequences, an isolated nucleic acid comprising a nucleotide sequence of at least 8 nucleotides that hybridizes under high stringency conditions to SEQ ID NO: 2580, an isolated nucleic acid comprising a nucleotide

sequence, wherein the nucleotide sequence hybridizes under high stringency conditions to SEQ ID NO: 2580 or fragments (all these are viewed as fragments/variants) and said fragments/variants having a specific function. The specification does not disclose immunogenic composition for the treatment or prevention of *S.epidermidis* infection. Therefore, said fragments/variants or immunogenic composition for the treatment or prevention of *S.epidermidis* infection as claimed do not meet the guidelines on written description.

The specification fails to disclose any deletion or change in a polynucleotide sequence, SEQ.ID.NO: 2580 to obtain fragments/variants that could hybridizes to the sequence presented in the SEQ ID NO: 2580. The specification does not describe any use of said fragments/variants as claimed (comprising, open language) in identifying *S. epidermidis.* None of the above polypeptides meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, the specification fails to teach the fragments/variants of nucleic acid or immunogenic composition for the treatment or prevention of *S.epidermidis* infection and does not satisfy the written description guidelines because the claimed fragments/variants encoded by have not been disclosed in this application. In addition, an isolated nucleic acid comprising (open language) a sequence SEQ.ID.NO: 2580 plus unlimited and unknown nucleic acid would result in an unknown nucleic acid without sufficient structure and completely lacking identifying characteristics such as function. Thus, nucleic acid fragments/variants as claimed are broader

than the SEQ.ID.NO: 2580 and do not appear to have sufficient structural characterization and lack any identifying characteristics (function). The specification fails to teach the structure or relevant identifying characteristics of said fragments/variants, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chugai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

10. Claims 1-13 and 32 are rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence as set forth in SEQ.ID.NO: 2580 encoding the *S.epidermidis* polypeptide comprising the amino acid sequence as set forth in SEQ.ID.NO: 6352, an isolated nucleic acid sequence comprising the nucleic acid sequence SEQ.ID.NO: 2580 and an immunogenic composition comprising said isolated sequences nucleotide sequence SEQ.ID.NO: 2580, encoding the *S.epidermidis* polypeptide comprising the amino acid sequence as set forth in SEQ.ID.NO: 6352 does not reasonably provide enablement for an isolated nucleic acid or immunogenic composition for the treatment or prevention of *S.epidermidis* comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide comprising SEQ ID NO: 6352, an isolated nucleic acid sequence comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide or fragment thereof , wherein said nucleic acid is SEQ ID NO: 2580, an isolated nucleic acid comprising a nucleotide sequence of at least 8 nucleotides that hybridizes under high stringency conditions to SEQ ID NO: 2580 or an isolated nucleic acid comprising a nucleotide sequence , wherein the nucleotide sequence

hybridizes under high stringency conditions to SEQ ID NO: 2580 or its complements (all these are viewed as fragments/variants) . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims have been discussed supra.

The specification fails to provide an enabling disclosure for the full scope of claimed nucleic acids as discussed above because it fails to provide any guidance regarding how to make and use said isolated nucleic acid or isolated nucleic acid encoding a polypeptide.

The instant claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the invention is related to genomic cloning of *S.epidermidis* strain, 18972 in an expression vector. Several genomic nucleic acid sequences and the encoding polypeptides have been disclosed in the specification.

The state of the art indicates that *S.epidermidis (*gram positive bacteria*)* is a coagulase negative *Staphylococci (*CoNS*)* present in normal skin flora and is frequently isolated bacteria in the clinical laboratories (Wieser M, Int .J. Syst. Evol. Microbiol. 2000 May;50 Pt 3:1087-93). This bacterium is frequently associated with bacteremia and post catheterization infections and recognized as important nosocomial pathogen. However, identification of gram positive,

coagulase negative *S.epidermidis* bacterial infection from other known species like *S.aureus* is still a problem and DNA based assays are still in the developmental stage only.

The current invention discloses an isolated nucleic acid comprising the nucleic acid sequence SEQ.ID.NO: 2580 and an isolated nucleic acid sequence encoding *S.epidermidis* polypeptide comprising the amino acid sequence SEQ.ID.NO: 6352. The specification fails to disclose how to make and use an isolated nucleic acid or immunogenic composition comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide comprising SEQ ID NO: 6352, an isolated nucleic acid sequence comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide or fragment thereof, wherein said nucleic acid is SEQ ID NO: 2580 or immunogenic composition. The specification lacks guidance how an isolated nucleic acid comprising a nucleotide sequence of at least 8 nucleotides plus other nucleic acid sequence would hybridize under high stringency conditions to SEQ ID NO: 2580 or an isolated nucleic acid comprising a nucleotide sequence, wherein the nucleotide sequence hybridizes under high stringency conditions to SEQ ID NO: 2580 or its complements (all these are viewed as fragments/variants). The specification provides no disclosure of said fragments/variants with a specific function. These fragments have not been shown to be positively identifying *S.epidermidis* infection.

These nucleic acid sequences are broadly claimed as an isolated DNA sequence encoding a polypeptide comprising SEQ.ID.NO: 6352 plus unlimited/ unknown sequences, isolated nucleic acid comprising SEQ.ID.NO: 2580 plus unlimited/ unknown sequences. However, the art in bacteriology teaches modifications in a protein for example, replacement of tyrosine 158 (Y158) to phenylalanine (Y158F) resulted in decrease in K_{cat} catalytic activity of InhA, the enoyl-ACP from *M.tuberculosis* (see abstract and tables 2-3 (Biochemistry 1999, Parikh et al, 38; 13623-13633). Further, modification of histidines with diethylpyrocarbonate has been shown to reduce the hemolytic activity of alpha-toxin (Infect Immun. 1994 May; 62(5):

1843-7) of *Staphylococcus aureus*. In addition, it is known that (see, Antimicrobial Agents and Chemotherapy, March 2001, p. 805-809, Vol. 45, No. 3) Sulfonamide resistance in *Streptococcus pneumoniae* is due to changes in the folP (*sulA*) gene coding for dihydropteroate synthase (DHPS). The emergence of Clarithromycin resistant *S.epidermidis* (Emerging Infectious Diseases 2005, Vol 11, (9) 1389-1393) infection in clinical patients indicates that resistant variants are developed. These references teach the changes made in the gene affect the function of the protein and leads to the development of drug resistant bacteria.

The specification fails to disclose nucleic acid fragments/variants/variants or polypeptide fragments/variants encoded by the nucleotide sequence of SEQ ID N0: 2580 and immunogenic composition for the treatment or prevention of *S.epidermidis* infection comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide comprising SEQ ID NO: 6352 and a nucleotide sequence of SEQ ID N0: 2580 and said polypeptide fragments The specification fails to teach the critical protein residues involved in this function of the protein encoded by SEQ ID N0: 2580, such that the skilled artisan is provided no guidance to test, screen or make the nucleic acid sequence variants of SEQ ID N0: 2580 or encoding variants of polypeptide 6352.

It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases (for example, Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding enablement. Several publications as shown below document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be

found to be conserved over biomolecules of related function upon a significant amount of further research. The following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al. [BioEssays, Volume 18, Number 12, pages 973-981(1996)]; Wells et al. [Journal of Leukocyte Biology, Volume 61, Number 5, pages 545-550 (1997)]; and Russell et al. [Journal of Molecular Biology, Volume 244, pages 332-350 (1994)]. One of skill in the art would be reduced to merely randomly altering nucleic acids, which would lead to unpredictable results regarding the functional activity of the protein.

Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et

al. (Mol. Microbiol. 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis in proteins and they differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. The specification has not taught which residues of the nucleotide sequence of SEQ ID N0: 2580 can be varied and still achieve a protein that is functional as claimed. Further, random insertions, deletions and changes to a nucleotide sequence do not provide guidance to make a related protein. The actual structure or other relevant identifying characteristics of each nucleic acid that encodes a variant protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the substitutions, insertions or deletions as compared to SEQ ID N0: 2580) and testing each to determine whether it encodes a protein variant having function. If there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention However, the specification fails to provide the function of the full-length protein and immunogenic composition for the prevention and treatment of *S.epidermidis* infection comprising said protein or its fragments.

Moreover, from the definition of Applicants' invention as set forth in the specification, it is unclear exactly what the composition of any protein will be if it is expressed by a nucleic acid which has the claimed fragments. For, example, if one nucleotide is deleted or inserted at a single place within the coding sequence, all the codons down stream of that insertion or deletion will be frame shifted. If that frame shift takes place near the 5' end of the gene, it is highly likely that the protein expressed will have little in common structurally or functionally with the protein encoded by the nucleic acid of SEQ ID N0: 2580. The specification fails to provide the protein disclosed as SEQ ID N0: 6352 encoded by the nucleic acid of SEQ ID N0: 2580, has specific

biological properties dictated by the structure of the protein and the corresponding structure of the structural nucleotide sequence which encodes it. There must be some nexus between the structure of a nucleotide sequence and the structure of the protein encoded, and the function of that encoded protein. However, function cannot be predicted from the modification of the structure of the gene sequence or in this case the nucleotide sequence encoding the protein. The specification has not shown that, by modifying a reference sequence encoding a reference polypeptide as claimed, will automatically predict the production of a polypeptide for use in any assay. The specification does not set forth the general tolerance to substitutions, where substitutions could be made to obtain equivalent protein variant. Since, the specification lacks support for any variant which has the ability to function as claimed, it is not enabled for this broad fragment/variant language because it fails to enable the skilled artisan to envision the detailed chemical structure of the polypeptide for use. In view of the lack of support for protein fragment/variant encoded by the nucleic acid fragment/variant of SEQ ID N0: 2580 that functions equivalently as claimed full length protein and the corresponding nucleic acid sequence, the lack of enabling description of how to make functionally equivalent polypeptide fragment/variant, the unpredictability associated with making and using the myriad of functionally equivalent fragment/variant encompassed in the scope of the claims as set forth above, the lack of teaching for variation of the nucleic acid for routine experimentation, the lack of an assay to screen for fragment/variant, lack of working examples commensurate in scope with the instant claims, the skilled artisan would be forced into undue experimentation to practice (i.e. make and use) the broadly claimed nucleic acid fragment/variant of the invention.

Claim Rejections - 35 USC 112, second paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is vague in reciting "an isolated nucleic acid consisting of SEQ.ID.NO: 2580" because isolated nucleic acid does not contain SEQ.ID.NO: 2580. Therefore, recitation of an isolated polynucleic acid consisting of the nucleic acid sequence as set forth in SEQ.ID.NO: 2580 is proper.

Please note: An isolated polynucleic acid consists nucleic acids. The structure of the polynucleic acid is identified by a sequence identification number (i.e., SEQ.ID.NO).

Claim 34 is vague in reciting "an isolated nucleic acid consisting of a nucleic acid encoding SEQ.ID.NO: 6352 " because an isolated nucleic acid consisting of a nucleic acid does not encode SEQ.ID.NO: 6352. Therefore, recitation of an isolated polynucleic acid consisting of the nucleic acid sequence that encodes the amino acid sequence as set forth in SEQ.ID.NO: 6352 is proper.

Claim Rejections - 35 U. S. C. § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 1, 5, 9, 10 and 32 are rejected under 35 U.5.C. 102(b) as being clearly anticipated by Goh et al Clin Microbiol. 1996 Apr;34(4):818-23.

The claims are drawn to an isolated nucleic acid or immunogenic composition comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide comprising SEQ ID NO: 6352, an isolated nucleic acid sequence comprising a nucleotide sequence encoding a *S.epidermidis* polypeptide or fragment thereof, wherein said nucleic acid is SEQ ID NO: 2580. Claims are also directed to an isolated nucleic acid comprising a nucleotide sequence of at least 8 nucleotides that hybridizes under high stringency conditions to SEQ ID NO: 2580, an isolated nucleic acid comprising a nucleotide sequence, wherein the nucleotide sequence hybridizes under high stringency conditions to SEQ ID NO: 2580 or its complements, a recombinant expression vector and host cell comprising said sequences.

The examiner is interpreting "a nucleic acid sequence encoding a S.epidermidis polypeptide" as any nucleic acid encoding any S.epidermidis polypeptide that is less than the full length polypeptide.

The transitional phrase or term "comprises" similar to terms such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Molecular Research Corp. v. CBS, Inc., 793 F2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App.1948)* ("comprising" leaves "the claim open. for the inclusion of unspecified ingredients even in major amounts". On the other hand, the limitation "consisting of represents closed claim language and excludes any element, step, or ingredient not specified in the claim. In *re Gray, 53 F. 2d 520, II USPQ 255 (CCPA 1931); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948).*

Goh et al disclose an isolated nucleic acid molecule amplified by PCR, encoding a portion of the 60-kDa protein (see table 1, figure 1 and 2) from *Staphylococcus epidermidis* using a set of universal degenerate primers, a 600-bp oligomer. However, when used as a DNA probe, the 600-bp PCR product generated from S. epidermidis failed to cross-hybridize under high-stringency conditions with the genomic DNA of S. aureus and vice versa. It is inherent that the PCR product as shown in table 1. Figure 1 and 2 contains the claimed isolated nucleic acid SEQ.ID.NO: 2580 and encodes polypeptide SEQ.ID.NO: 6352 because the PCR product is

specific for *S.epidermidis* and the 600 base pair PCR product (nucleic acid product) appears to be containing the claimed nucleic acid that encodes the polypeptide having less than 60kD protein (i.e., claimed polypeptide is approximately 40kD). In the absence of evidence to the contrary the disclosed prior art PCR product (nucleic acid) would inherently contains the claimed nucleic acid as the use of PCR coupled with restriction endonuclease analysis of PCR product has proven to be sensitive and specific in the art.

Since the Office does not have the facilities for examining and comparing applicant's nucleic acid with the nucleic acid of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See In re Best, 56 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594. Characteristics such as SEQ.ID.NO 2530 etc is considered as an inherent property of the PCR product.

16. Claims 1, 5, 9, 10 and 32 are rejected under 35 U.5.C. 102(e) as being clearly anticipated by Ohno et al, US Patent 5,770,375.

Ohno et al disclose a probe comprising a nucleic acid sequence SEQ.ID.NO: 5 consisting of contiguous nucleotides of AAAAAAAAT (see SEQ.ID.NO: 5, nucleotides from position 1643-1651, example 2, column 4, lines 67 through column 5). This reads on the claimed probe (claim 9) comprising nucleic acid sequence consisting of at least 8 nucleotides of SEQ.ID.NO: 2580 because the probe comprises a nucleic acid sequence consisting of 100% identical at least 8 contiguous nucleotides (position 259-267) of SEQ.ID.NO: 2580. The same nucleic acid sequence reads on claims 10 and 32 as the disclosed sequence consisting of 9 nucleotides that are 100% identical to the at least 8 contiguous nucleic acids of SEQ.ID.NO: 2580 and has been shown to be hybridizing (see column 5). Similarly the disclosed nucleic acid

reads on fragments as in claim 5 and a nucleotide sequence (less than full length or more than one nucleic acid) as in claim 1. The prior art anticipated the claimed invention.

Relevant Prior Art

18. The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

Martineau F, J Clin Microbiol. 1996 Dec: 34(12): 2888-93 teach *Staphylococcus epidermidis* is an aerobic gram-positive coccus that is now recognized among the coagulase-negative staphylococci as an etiological agent with an important range of pathogenicity in humans. Several diagnostic kits based on biochemical or immunological reactions can efficiently identify Staphylococcus aureus. However, these tests are often unreliable for the identification of coagulase-negative staphylococcal species including S. epidermidis. Since DNA-based assays for the species-specific identification of S. epidermidis remain unavailable. On the basis of the results of hybridization assays with clones randomly selected from an S. epidermidis genomic library, we identified a chromosomal DNA fragment which is specific and 100% ubiquitous for the identification of S. epidermidis. This 705-bp fragment was sequenced and used to design PCR amplification primers. PCR assays with the selected primers were also highly specific and ubiquitous for the identification from bacterial cultures of clinical isolates of S. epidermidis from a variety of anatomic sites.

Risitano DC, Minerva Anestesiol. 2005 Sep; 71(9): 561-4 teach bacterial infection is the most important clinical complication associated with the use of central venous catheters (CVCs). Despite the efforts for the optimization of the materials that are more and more biocompatible, the presence of a foreign body in the organism is an ideal substratum for the microbial colonization. The Catheter-Related-Bloodstream-Infections (CRBI) involve a prolongation of recovery stay, the increase in costs of hospitalization and an increase in morbidity and mortality. The infections are caused by: Staphylococcus aureus and Staphylococcus epidermidis (60%), other bacteria (Enterococcus faecalis and Faecium, Pseudomonas aeruginosa; 25%) and among fungi by Candida albicans and Parapsilosis (15%).

Dunne WM Jr, Clin Microbiol Rev. 2002 Apr; 15(2): 155-66 teach the process of surface adhesion and biofilm development is a survival strategy employed by virtually all bacteria and refined over millions of years. This process is designed to anchor microorganisms in a nutritionally advantageous environment and to permit their escape to greener pastures when essential growth factors have been exhausted. Bacterial attachment to a surface can be divided into several distinct phases, including primary and reversible adhesion, secondary and irreversible adhesion, and biofilm formation.

O'Gara JP, **Humphreys H**. J Med Microbiol. 2001 Jul;50(7):582-7 teach the coagulase-negative staphylococci and, in particular, Staphylococcus epidermidis, have emerged as major nosocomial pathogens associated with infections of implanted medical devices. These organisms, which are among the most prevalent bacteria of the human skin and mucous membrane microflora, present unique problems in the diagnosis and treatment of infections

involving biofilm formation on implanted biomaterials. An extracellular polysaccharide adhesin represents a key virulence determinant in S. epidermidis and is required for biofilm formation.

DRUG RESISTANCE:
Ip D, Yam SK, Chen CK, J Orthop Surg (Hong Kong). 2005 Aug; 13(2): 125-30 teach the causative organisms isolated from infected hip and knee replacements, knee arthroplasties due to bacterial infection at Pamela Youde Nethersole Eastern Hospital in Hong Kong between 1995 and 2003. The male to female ratio was 1:2, and the mean age of patients was 70 years (range, 54-82 years). The mean duration of follow-up was 3.8 years (range, 1.1-8.3 years). No patient was lost to follow-up. All 14 revision knee patients had previously undergone cemented and patella-resurfacing total knee arthroplasties. Of the 22 revision hip patients, 9 had cementless, 6 had cemented, and 7 had hybrid total hip arthroplasties previously. RESULTS. None of the bacteria isolated from 1995 to 1996 were multiple-drug resistant. Subsequently, however, most of the isolates were multiple-drug resistant, with methicillin-resistant Staphylococcus aureus (MRSA) being the most common. Half of the isolates of Staphylococcus epidermidis and Escherichia coli demonstrated multiple-drug resistance. The incidence of positive culture in revision hip patients was 59%, 46% of which were MRSA. All 13 revision hips with positive cultures showed chronic sepsis: 4 occurred within one year and 10 occurred 2 or more years after the index arthroplasty. The incidence of positive culture in revision knee patients was 57%, 46% of which were MRSA. All 8 revision knees with positive cultures showed chronic sepsis: 3 occurred within one year, 5 occurred 2 or more years after the index arthroplasty.. Thus this study discloses multiple-drug-resistant bacteria isolated from periprosthetic infections around total hip and knee prostheses.

Gill SR, Fouts DE et al Bacteriol. 2005 Apr: 187(7): 2426-38 teach Staphylococcus aureus is an opportunistic pathogen and the major causative agent of numerous hospital- and community-acquired infections. Staphylococcus epidermidis has emerged as a causative agent of infections often associated with implanted medical devices. We have sequenced the approximately 2.8-Mb genome of S. aureus COL, an early methicillin-resistant isolate, and the approximately 2.6-Mb genome of S. epidermidis RP62a, a methicillin-resistant biofilm isolate. Comparative analysis of these and other staphylococcal genomes was used to explore the evolution of virulence and resistance between these two species. The S. aureus and S. epidermidis genomes are systemic throughout their lengths and share a core set of 1,681 open reading frames. Genome islands in nonsyntenic regions are the primary source of variations in pathogenicity and resistance. Gene transfer between staphylococci and low-GC-content gram-positive bacteria appears to have shaped their virulence and resistance profiles. Integrated plasmids in S. epidermidis carry genes encoding resistance to cadmium and species-specific LPXTG surface proteins. A novel genome island encodes multiple phenol-soluble modulins, a potential S. epidermidis virulence factor. S. epidermidis contains the cap operon, encoding the polyglutamate capsule, a major virulence factor in Bacillus anthracis. Additional phenotypic differences are likely the result of single nucleotide polymorphisms, which are most numerous in cell envelope proteins. Overall differences in pathogenicity can be attributed to genome islands in S. aureus, which encode enterotoxins, exotoxins, leukocidins, and leukotoxins not found in S. epidermidis.

Remarks

14. No claims are allowed.

Conclusion

15. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D

NITA MINNIFIELD
PRIMARY EXAMINER
11-10-05